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| EXAMINER | |
|---|---|
| KELLY, ROBERT M | |

| ART UNIT | PAPER NUMBER |
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| 1632 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/608,997 | PROCKOP ET AL. | |
| | Examiner | Art Unit | |
| | Robert M. Kelly | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response to restriction requirement and amendments and arguments of 03/25/05 are entered.

Applicant's copy of the second preliminary amendment of 10/10/03 and copy of receipt of such amendment, submitted 03/25/05, are entered into the record.

Claims 19-20 were cancelled prior to the restriction requirement of 2/23/05.

Claims 1, 9, 11, and 16 are amended.

Claims 1-18 remain pending.

### *Election/Restrictions*

Prior to addressing Applicant's election, it should be noted that the preliminary amendment of 10/10/03 was not present in the Application file at the time of the Examiner's restriction requirement of 2/23/05. During a telephone conversation, Mr. Nguyen, attorney of record, made the Examiner aware of such preliminary amendment, and reviewed the claims, as they were amended, in such preliminary amendment, with the Examiner. The Examiner agreed that the amendments did not effect the restriction requirement, and that Applicant would provide another copy of such preliminary amendment, along with evidence that such amendment was submitted to the office (i.e., postcard receipt), and a synopsis of this conversation. Applicant has submitted the copy of the preliminary amendment in question, along with a copy of the postcard receipt, and such synopsis of the conversation, in the response to election of 3/25/05. Moreover, upon review of the amendments, the Examiner maintains that the restriction requirement is unaltered due to the preliminary amendment.

Therefore, the restriction requirement of 2/23/05 is maintained on the claims as present at the second preliminary amendment of 10/10/03, of which Applicant has presented a new copy of such amendment with the election of 3/25/05.

Applicant's election without traverse of Group I, claims 1-8 and 16-18, drawn to a method of directing the differentiation of an isolated stromal cell into a neural cell in a human patient suffering from a disease, disorder, or condition of the central nervous system, in the reply filed on 3/25/05 is acknowledged.

Claims 9-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/25/05.

***Drawings***

The drawings are objected to under 37 CFR 1.83(a) because they fail to show, for figure 6, which sections are at 4, 14, 30, or 72 days, as described in the specification (p. 8, paragraph 2). Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief

description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Priority***

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence(s) of the specification or in an application data sheet by identifying the prior application by application number (37 CFR 1.78(a)(2) and (a)(5)). If the prior application is a non-provisional application, the specific reference must also include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Applicant's claim to priority is objected-to because there exists no application data sheet referencing Applicant's priority information, and the specification makes reference to:

(1) US/PCT96/04407, as a CIP, without stating its publication number (i.e., WO 96/30031);

(2) US Application No 08/412,066, as a CON, without stating its issued patent number and issue date (i.e., US Pat. No. 5,716,616 on 2/10/98); and

(3) U.S. Application No. 09/028,395, filed 2/24/98, without stating its issued patent number and issue date (i.e., U.S. Patent No. 6,653,134 on 11/25/03).

Additionally, even if Applicant were to comply with the formal requirements for priority, Applicant's priority to US/PCT96/04407, which was published as WO 96/30031; U.S. Application No. 08/412,066, which was patented as U.S. Patent No. 5,716,616, and U.S. Provisional Application No. 60/006,627 are denied because these applications do not provide a disclosure commensurate with the requirements of 35 USC 112, first paragraph. To wit, none of these applications disclose the differentiation of stromal cells into any form of brain cell, but, instead disclose the use of these cells in replacing the individual's bone, cartilage, or lung cells (e.g., U.S. Patent No. 5,716,616, col. 3, paragraph 3). Therefore, in no way would the Artisan believe Applicant was in possession of the differentiation of any stromal cell into any neural cell at all, much less *in vivo*.

Therefore, Applicant only has priority to Application No. 09/028,395, filed 2/24/98, and patented as U.S. Patent No. 6,653,134 on 11/25/03.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's newly-amended claims are drawn to methods of directing the differentiation of an isolated stromal cell into a neural cell in a human patient. Such method of directing the differentiation of a stromal cell *in vivo* is not contemplated by the specification and claims as filed, and as further evidence, Applicant's specification defines "directing differentiation" as "construed to mean the induction of a differentiated phenotype in an undifferentiated cell by coculturing the undifferentiated cell in the presence of a substantially homogeneous population of differentiated cells." (SPECIFICATION, p. 14, paragraph 2). As such, the art recognized term of coculturing means *in vitro*, and even if it does not, the brain tissues into which the cell would be placed by the method are not substantially homogeneous, and as such, the method would not meet the requirements of co-culturing, even if co-culturing were an art-recognized term for *in vivo* transplantation of cells.

Hence, Claims 1-8 and 16-18 encompass new matter.

***Claim Rejections - 35 USC § 112***

Claims 1-8 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple

factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

**The Breadth of the Claims**

Applicant's claims are broad in scope which is found not enabled because the experimentation required to find the working embodiments encompassed by would require undue experimentation on the part of the Artisan, because the breadth claimed is fraught with difficulties that lead to a lack of reasonable predictability. Below is a synopsis of the breadth of Applicant's claimed invention.

Claims 1-8 and 16-18 encompass a method of directing the differentiation of any isolated stromal cell into any neural cell in any human patient suffering from any disease, any disorder, or

any condition of any part of the central nervous system, comprising obtaining a bone marrow sample from any human donor, isolating stromal cells from the bone marrow, and administering, by any method, the isolated stromal cells to any part of the central nervous system of the patient. Claim 2 limits the donor to any syngenic donor not suffering from any disease, disorder, or condition of the central nervous system. Claim 3 limits the treatment to autologous cell therapy. Claim 4 limits the disease/disorder/condition to any genetic disease, any tumor, any trauma, or stroke. Claim 5 limits the disease/disorder/condition to injury to any cell or tissue of the central nervous system. Claim 6 limits the disease/disorder/condition to any brain tumor. Claim 7 limits the isolated stromal cells to remaining present or replicating in the central nervous system. Claim 8 requires the stromal cells to be cultured *in vitro* for a period of time before administration. Claim 16 requires that, prior to administration, the stromal cells to be pre-differentiated by coculture in the presence of any substantially homogeneous population of differentiated cells, whereby the stromal cells differentiate and acquire the phenotypic character of the differentiated cells. Claim 17 requires that, prior to administration, at least one of: (i) culturing *in vitro*; (ii) introducing any nucleic acid into the cells; and/or (iii) the cells are predifferentiated. Claim 18 requires that the cells be immunologically isolated by any method.

Moreover, it should be noted that although Applicant is claiming a method of directing differentiation *in vivo* of such bone marrow stromal cells, the only use disclosed for such differentiation of stromal cells is that of therapy for any disease of the central nervous system (e.g., SPECIFICATION, p. 5). Hence, although requiring that the cells differentiate *in vivo*, the claims also require that such is reasonably predictable to treat diseases.

Because of the breadth of diseases, breadth of transgenes, breadth of methods of administration, breadth of predifferentiations, breadth of immunological isolations, and breadth of locations of the diseases within the central nervous system, these claims are not enabled. As will be shown below, due to the lack of reasonable predictability in the field, and lack of direction, guidance and examples provided by Applicant to overcome such lack of reasonable predictability, the Artisan would have to perform undue experimentation to find the working embodiments embraced by Applicant's claims.

**The Nature of the Invention and State of the Prior Art**

Applicant's invention is in the nature of somatic cell therapy and *ex vivo* gene therapy for disorders of the central nervous system in humans.

With regard to somatic cell therapy, as well as *ex vivo* gene therapy, a number of problems exist with regard to the route of administration, the transplanting of enough cells, and expression of enough transgene in gene therapy, and an effect for a long enough period of time to effect treatment. To wit, Bartley, et al. (2003) Expert Opin. Biol. Ther., 3(4): 541-49 provides an overview for stem cell therapy for cerebral palsy (TITLE) which will suffice to delineate some of the problems with such therapies. Bartley only recognizes that two methods of administration appear to be feasible for treatment of cerebral palsy, those of intravenous or direct injection (p. 542, col. 1, paragraph 4), neither of which, as will be shown below, is yet to be reasonably predictive of delivering enough cells to the site of action. In stating such, Bartley also recognizes that it is not reasonably predictable that any therapy can be effected with such cells injected into the vasculature, due to the permeability of the blood-brain barrier (Id.). Hence, on top of only two methods of administration being feasible to produce therapeutic effects, Bartley also

recognizes that it is not necessarily reasonably predictable that vascular administration would produce a therapeutic effect. Next, with palsy, as with many diseases of the central nervous systems, patients have differing effects with regard to amounts of grey or white matter (and specific cell types and ratios of cell types) being lost, and therefore, the type of cell used to effect such therapy must be able to reasonably predictably differentiate into each of the cell types in the correct proportions (p. 542, col. 1, paragraph 5), and, in fact, it is not even reasonably predictable which or whether both need to be replaced in any particular instance of the disorder (Id.). Therefore, even for any subset of diseases of the CNS, it is not reasonably predictable which cells to replace in the first place, much less whether marrow stromal cells can do so for each cell type and in the correct proportions. Moreover, mere replacement of certain forms of cells may not effect a disease, as in palsy, where Bartley demonstrates that it is not reasonably predictable that replacement of myelin, without replacement of the axons themselves, would facilitate any functional improvement (p. 542, col. 2, paragraph 2).

Bartley also indicates that the choice of cell type, stage of differentiation, and derivation a critical issue, indicating the specific stem cell may not be efficacious for any particular form of palsy, much less any disorder of the central nervous system (Id., paragraph 3). With regard to bone marrow stromal cells, Bartley recognizes that crude bone marrow can generate neural progenitor cells in culture and individuals at autopsy who had received bone marrow transplants have been shown to comprise neurons arising from the transplant (p. 543, col. 2, paragraph 4). However, such evidence does not enable Applicant's invention, because it is post-filing evidence, citing articles that are post-filing evidence, and these articles teach *in vitro* differentiation, and the patients had whole bone marrow transplants, not stromal cell implants.

Various other post-filing evidence is also cited to demonstrate *in vitro* differentiation of stromal cells, implantation of bone marrow, and transplantation and migration of stromal cells into the forebrain and cerebellum of neonatal mice after transplantation into the lateral ventricle (Id., paragraph 5). However, such evidence is similarly not enabling for Applicant, as the articles cited are post-filing evidence, and the neonatal mice do not have a fully-formed blood-brain barrier; therefore, this would not reflect the ability to treat any central nervous system part in a human, as humans have fully-developed blood-brain barriers. However, Bartley also provides numerous lines of evidence to indicate that marrow stromal cells can differentiate into various tissues and that such **may** be able to occur *in vivo* (p. 544, col. 1), but also there exists conflicting data (Id., paragraph 2). With regard to method of administration, Bartley again emphasizes that it would seem unlikely that intravenous injection would get enough cells to the site to effect treatment (p. 544, paragraph bridging columns). Further, Bartley questions the use of undifferentiated cells, and indicates that it is not reasonably predictable yet, requiring further exaperimentation, to determine the state of differentiation which should be applied in any particular treatment (p. 544, last paragraph). Furthermore, it is noted that even when these cell differentiate in some fashion, it is not clear whether such is the source of the therapeutic effect, or whether recovery is mediated by some other substance elaborated by the implanted cells (p. 545, col. 1, paragraph 2), and therefore, Applicant's requirement that the cells differentiate may actually not cause any therapeutic effect at all. Moreover, other results indicate that improvements in function may not be linked to the implantation of the cells themselves (Id., col. 2, paragraph 1), making the results suspect for any therapy associated with stromal cell therapy

to the brain. Also, Bartley, even when a finding seems positive, indicates the need for further confirmation of the information before the data can be fully accepted (Id.).

Bartley also indicates that immune reactions may occur, which may be detrimental (Id., paragraph 2). This can further be interpreted that such immune reactions may kill any transplanted cells before they could effect therapy.

In conclusion, Bartley indicates that while the data is encouraging, extensive experimentation is still required before human treatment will be feasible (p. 545, col. 2, paragraph 2; p. 546, col. 1). Clearly, Bartley is indicating that somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans at this point, which is after Applicant's filing date.

Hence, from reviewing Bartley, the Artisan would only be able to make one conclusion: somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans. This is because it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place;

and it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen.

Savitz, et al. (2003) J. Cardiovasc. Nurs., 18(1): 57-61 further demonstrates that these bone marrow stromal cells are not yet reasonably predicted to treat human CNS diseases in another context: that of stroke recovery (TITLE). While focusing on neural progenitors and fetal stem cells, Savitz discusses the possible use of stromal cells as another "potential" graft source for the treatment of strokes (p. 59). In it, Savits comments on Li, demonstrating "intriguing therapeutic possibilities" through these preliminary results (p. 59, col. 2, paragraph 2). However, Savitz also concludes that "much work lies ahead" because it remains largely unknown to what extent the different stem or progenitor cells differentiate into neurons or other brain cells, echoing the seniments expressed in Bartley (p. 60, col. 1). Furthermore, it is unknown if any particular stem cell would yield the correct percentage of progeny needed to reconstruct specific brain regions, what factors within the brain will support or the viability of such grafts, and will they integrate safely, or will immune responses destroy the graft before therapy can be effected (p. 60, paragraph bridging columns). Hence, as Savitz concludes "Answering these and many other questions will require **extensive** investigation in order to yield useful data from which to draw practical information" (Last sentence, emphasis added).

Therefore, Savitz, in discussing a different disease, stroke, also concludes that much more experimentation is needed to elucidate the various problems of such somatic cell therapy for brain disorders. Such is also clearly linked to method of administration, the type of stem cell, whether it will differentiate properly, whether it will be destroyed by immune reactions before therapy is effected, and whether enough cells will be present and have enough of an effect for a

long enough period of time to effect treatment, and/or whether the cells will actually integrate and replace the dysfunctional tissues of the brain.

In terms of gene therapy effected with such cells, similar problems exist, compounded by the requirement of the transgene to produce enough mRNA, given the number and concentration of stromal cells that reach the site, and enough protein therefrom, and the protein then must be properly trafficked to reach the proper site of action in enough amounts for a long enough period of time to effect treatment. Furthermore, given Applicant's lack of description as to which genes and promoters to use in any particular therapy, and given that, as Bartley has shown, no gene may be required for any particular disease, it would require undue experimentation to determine which gene to use, and which promoters and other regulatory elements to use in the treatment of any particular disease. Moreover, Horn, et al. (2004) Molec. Ther., 10(3): 417-431, demonstrates that the small animal studies, in which most experiments have been performed to date (e.g., rodents), even if they are efficacious of treating a particular disease, are not reasonably predictive of treatment in humans. Horn discusses the potential of hematopoietic stem cells, stating that the use of such in stem cell therapy has great promise for the future, but does not recognize any currently reasonably predictable treatment for such stem cells (p. 417, paragraph bridging). (It should be noted that while the Examiner acknowledges that the reference is drawn specifically to treating central nervous system disorders, the issues to be raised (below) extend to all forms of treatment by stem cell gene transfer, and not just the treatment of the hematopoeitic system; and if Applicant wishes to take issue with any of these art-recognized problems, the Examiner requests a scientific explanation of why such issue is not pertinent to Applicant's claimed therapy.) Horn first demonstrates that in initial results, it was shown that mouse

hematopoeitic stem cells could be genetically modified with a degree of efficiency predicted to be therapeutic for many human diseases; however, in later experiments it became apparent that such therapy did not work in humans (p. 417, col. 2, paragraph 2). Hence, it is not reasonably predictable that mouse systems of gene therapy in stem cells is not predictable of therapy in humans. Next, Horn discusses the fact that large animal models may be better models for therapy in humans, but that such experiments are very labor intensive (p. 418). Moreover, xenotransplantation models are also found not to be reasonably predictive of such therapy (p. 419, col. 1, paragraph 1). Further, choice of vector to transform the stem cell is important, and no specific vector is found to be reasonably predictive of any specific therapy (pp. 419-420, paragraph bridging). Moreover, gene expression and silencing are often, and in a seemingly random fashion, problems which the art has yet to fix, which results are found to be linked to many things, including vector choice, conditions and length of culturing, and length of time and location into which the cells are transplanted (pp. 420-422). Hence, it is not reasonably predictable that through any particular set of conditions and vectors with any specific promoter and transgene, and cells, that the gene will be expressed for a long enough period of time to effect treatment. Immune responses to transgenes may also preclude treatment by killing the transplanted cells before therapy may be effected (p. 424, col. 1, paragraph 3-col. 2, paragraph 3). Also, similar to Bartley's conclusions, the source and differentiation state of the stem cell is critical and is not yet predictive of treatment of any particular disease (pp. 424-425, paragraph bridging). Further, while still not being considered reasonably predictable at this point, Horn emphasizes that large animals models are needed to be examined to determine therapy, and that the small animals used, as in Applicant's experiments (below), are definitely not reasonably

predictive of therapy in humans (pp. 426-427), and that such is due to, for example, the different endocrine signals and distinct stem cell pathways which larger animals have, which are different between the larger primates and the smaller ones (p 425, col. 1).

Lastly, with regard to immunologically isolated, if such cells are immunologically isolated, then the factors and such that the cells produce cannot reach the adjacent cells, and therefore no therapy could reasonably be effected in any particular disease, particularly if the disease requires the cells to differentitate into cells of the central nervous system as those cells would be required to become part of the CNS, and not just exist nearby. To put this in perspective, if you placed brain tissue within someone's brain, it is not predictable that the brain tissue would be part of the brain, but simply garbage inside the brain. The cells would need to integrate, and immunological isolation would inhibit such integration.

In reviewing the above references, it is clear that the artisan would find any particular stem cell therapy in humans not reasonably predictable because: it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions

will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

**The Level of Predictability in the Art**

Because of the art, as shown above, does not disclose any therapy of any central nervous system disorder in a human, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

**The Level of One of Ordinary Skill in the Art at the Time of Invention**

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

**The Direction and Guidance Provided By Applicant**

Applicant's specification broadly discusses the treatment of neurological damage in many diseases and the potential for the use of stromal cells (pp. 1-5), a summary of the invention broadly tracking the claims (pp. 5-7), definitions (pp. 9-14), broad disclosure of stromal cells, where they are isolated from, and predictions of ability to treat disease (pp. 14-21), further broad

discussion of such cells with transgenes (pp. 21-25), culturing conditions (pp. 25-26), and administration methods and more culturing conditions (pp. 26-33).

However, such broad description does not constitute the specific direction and guidance the Artisan would require to reasonably predict whether, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

**The Existence of Working Examples**

Example 1 demonstrates that stromal cells may contribute to connective tissue differentiation. Example 2 demonstrates the conditions for culture and isolation of stromal cells. Example 4 demonstrates long-term expression of genes in such cells. Example 5 demonstrates expression of such genes in subcutaneous diffusion chambers. Example 7 demonstrates that after

direct administration of the stromal cells into rat brains, such cells may be found in the brains of rats for many weeks after administration, and migrate into various portions of the brain. Example 8 demonstrates that in the presence of astrocytes, the stromal cells exhibit a single marker of early astrocyte differentiation: glial fibrillary acidic protein.

Such examples however fall far short of the knowledge produced in the art, as described by the two articles provided above. They do not reasonably predict any therapy in humans for reasons given in the art and nature of the invention: mouse models and xenotransplantation in small animals is not reasonably predictive of any therapy in humans, even when cells produce physiologically relevant levels of genes (above). Moreover, they do nothing to overcome the lack of reasonable predictability it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that

immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

**Undue Experimentation**

Due to the reasons given in the last paragraph, the Artisan would have to perform undue experimentation to treat any particular disease, through any particular form of administration of such stromal cells, at any particular level of differentiation, with or without any particular transgene and promoter and other regulatory elements, with or without immunological isolation, to treat any particular instance of any disorder/disease/condition, due to the lack of reasonable predictability.

Such experimentation is considered extensive and undue.

**Conclusion**

Applicant's claimed invention is considered non-enabled for its whole scope due to the requirement for undue experimentation to find any particular working embodiment.

## *Conclusion*

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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